PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P 10471 PC	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DK 03/00231	International filing date *(day/month/year)* 08.04.2003	Priority date *(day/month/year)* 09.04.2002
International Patent Classification (IPC) or both national classification and IPC C07C275/28		
Applicant 7TM PHARMA A/S et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 19 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07.11.2003	12.07.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Jardon Alvarez, J Telephone No. +49 89 2399-8325

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00231

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-46, 49-56, 65-107, 111, 113-115	as originally filed
47, 48, 57-64, 108, 109, 110, 112	filed with telefax on 11.06.2004

Claims, Numbers

1-54	filed with telefax on 11.06.2004

Drawings, Sheets

1/1	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☒ the description, pages: 58,59,60,61,62,109

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-14,35-42

   because:

   ☒ the said international application, or the said claims Nos. 35-42 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-14

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-54
	No:	Claims	
Inventive step (IS)	Yes:	Claims	2,3-54(in part)
	No:	Claims	1,3-54(in part)
Industrial applicability (IA)	Yes:	Claims	1-34,43-54
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The International Preliminary Examination cannot be carried out in respect of subject-matter which is not covered by the search report (see Rule 66.1(e) PCT). Consequently claims 1 - 14 are examined only to the extent that they have been searched (see International Search Report, Box I.2).

2. Claims 35 - 42 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D2: US - 4 146 637
D3: WO - A - 01/21577

1. The subject-matter of claims 1 to 54 is novel (Article 33(2) PCT).

1.1. Document D2 discloses structurally related N-acyl substituted methoxy-benzamides (see claim 1 and Table I, compounds 14, 17 and 19) and pharmaceutical compositions having anti-inflammatory and anti-allergic activity (see claim 5).

The compounds disclosed in D2 have always a Cl group in the para-position to the $-OCH_3$ group. The compounds claimed in the amended claims of the present application do not longer cover such compounds because the definition of X has been limited to the groups hydrogen or fluorine. Thus D2 does not anticipate the subject-matter of the claims of the present application.

1.2. Document D3 discloses melanin-concentrating hormone antagonists of the formula (I) as given in claim 1 which embrace in part the compounds of the present application (see D3, claims). The compounds now claimed fall in part within the broad scope of the general formula defined in claim 1 of D3. There is

however neither a reference to the sub-group of the compounds now claimed or a single example of a compound falling within the scope of the claims of the present application. Therefore D3 is also not novelty destroying for the claims.

1.3. For these reasons the subject-matter of the claims 1 to 54 is novel (Article 33(2) PCT).

2. The subject-matter of the claims, insofar as it relates to compounds wherein the linker A is selected from the group of substituents as defined in claim 2, involves also an inventive step (Art. 33(3) PCT).

2.1. The closest prior art document, D3, discloses melanine-concentrating hormone antagonists which are useful for preventing or treating diseases such as obesity and related disorders (see claims).

The problem to be solved by the present application can be seen as to find further compounds having improved activity. The Applicant has provided experimental evidence to the Examining Authority showing that the compounds now claimed show a significantly increased affinity for the MCH receptor when compared with the closest structural compounds disclosed in D3.

Moreover the Applicant also has experimentally shown that some of the claimed compounds have increased activity when compared with structurally related compounds disclosed in D2.

There is no hint in the available prior art to this increased activity of some the claimed compounds and therefore an inventive step is acknowledged for such compounds (Article 33(3) PCT).

2.2. It is however noted that it is doubtful that all the compounds covered by the present claim 1 solve the above mentioned problem, that is to say that they are compounds having improved melanin-concentrating hormone modulating activity. Claim 1 embraces a huge number of compounds (see the definitions of A, Ar and Q) which have not yet been explored.

The compounds for which experimental data have been provided are urea derivatives or amides (see pages 112 - 114; see also experimental evidence submitted with telefax of 11.06.2004). Having in mind that in the medicament field

often small structural changes give rise to unexpected activity changes, a generalization of the results obtained with a few compounds to compounds having a quite different structure does not appear to be justified. It is therefore doubtful that all the alternatives covered by the broad scope of claim 1 would achieve the claimed effect.

2.3. The subject-matter of claim 2 is limited to compounds wherein the linker A has been limited to structures close to the compounds tested. It appears to be a fair generalization of the experimental evidence provided and therefore an inventive step is acknowledged for the subject-matter of claim 2 and all the reamining claims insofar as they depend on claim 2 (Article 33(3) PCT).

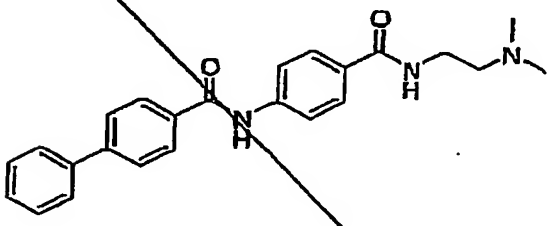
3. For the assessment of the present claims 35 - 42 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3.49 (m, 2H), 3.90 (s, 3H), 4.02 (br s, 2H), 6.20 (s, 1H), 6.34 (d, 1H), 7.91 (br s, 1H) and 8.02 (d, 1H).

To a solution of 4-biphenylcarbonyl chloride (0.26 g, 0.80 mmol) in dichloromethane (5 µl) under inert atmosphere was a solution of the above prepared compound in dichloromethane (3 µl) added the reaction mixture was stirred at room temperature for three days. The purification was performed according to the protocol for preparation of Ex 2 and the crude product was chromatographed (Al_2O_3, EtOAc/Heptane, 2:1) giving 0.10 g (30%) of the title product. ^1H NMR (300 MHz, $CDCl_3$): δ 1.82 (t, 2H), 2.30 (s, 6H), 2.44 (t, 2H), 3.55 (m, 2H), 4.04 (s, 3H), and 6.96 (d, 1H).

Example 4

Biphenyl-4-carboxylic acid [4-(2-dimethylamino-ethylcarbamoyl)-phenyl]-amide



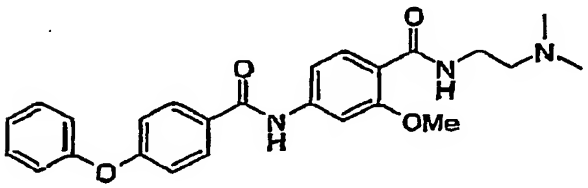
To a solution of 4-nitrobenzoyl chloride (0.50 g, 2.7 mmol) in dichloromethane (10 µl) were triethylamine (0.75 µl , 5.4 mmol) and *N,N*-dimethylethyldiamine added. The reaction mixture was stirred for three days before extraction with EtOAc and Na_2SO_4 (aq) was performed. The combined organic phases were dried, filtrated and evaporated. The crude product was dissolved in ethanol (10 µl) and Pd/C (40 mg, 20 % w/w) was added. The reaction mixture was stirred at room temperature under a hydrogen atmosphere over night. The catalyst was filtered off through a celite pad and the filtrate was concentrated *in vacuo* giving 0.32 g (56%) of 4-amino-*N*-(*N'*,*N'*-dimethylaminoethyl)benzamide.

To a solution of 4-biphenylcarbonyl chloride (0.47 g, 2.2 mmol) in dichloromethane (6 µl) under inert atmosphere were added triethylamine (0.4 µl , 2.9 mmol) and 4-amino-*N*-(*N'*,*N'*-dimethylaminoethyl)benzamide (0.3 g, 1.45 mmol) dissolved in dichloromethane (3 µl). The reaction mixture was stirred at room temperature for three days. An additional portion of dichloromethane (3 µl) and PS-trisamine (0.8 g, 3.38 mmol/g) were added to the reaction mixture and the stirring was continued for 2 h at room temperature. The resin was filtered off and rinsed twice with dichloromethane (2 x 3 µL) before extraction with EtOAc and Na_2SO_4 (aq) was performed. The combined organic phases were dried, filtrated and evaporated. The crude product was chromatographed (Silica,

~~dichloromethane/methanol/ammonia, 100:10:1) and recrystillazed (EtOAc) giving 0.176 g (31%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 6H), 2.74 (t, 2H), 4.19 (t, 2H), 7.90 (d, 2H).~~

Example 5

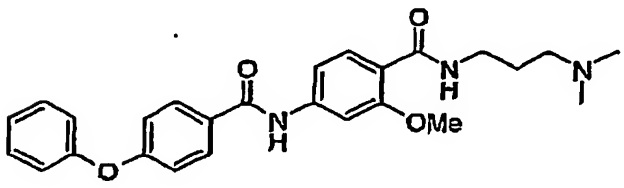
***N*-(2-Dimethylamino-ethyl)-2-methoxy-4-(4-phenoxy-benzoylamino)-benzamide**



In a flask were placed 4-phenoxy benzoic acid (27 mg, 0.13 mmol) and *N,N*-dimethylformamide (2 µL) and the flask was cooled to 0°C, whereupon EDAC (24 mg, 0.13 mmol) and HOBt (17 mg, 0.13 mmol) were added. The mixture was gently stirred for 20 minutes at room temperature before **Ex 1** (41 mg, 0.19 mmol) dissolved in *N,N*-dimethylformamide and DiPEA (22 µl, 0.13 mmol) were added. The reaction was continuously stirred three days before extraction with EtOAc and Na_2SO_4 (aq) was performed. The combined organic phases were dried, filtrated and evaporated. The crude product was chromatographed (Silica, dichloromethane/methanol/ammonia, 100:20:2) yielded 12 mg (20%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.48 (s, 6H), 2.77 (m, 2H), 3.68 (m, 2H), 4.03 (s, 3H), 8.16 (d, 1H), and 8.39 (br s, 1H).

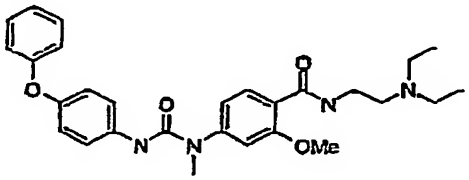
Example 6

***N*-(3-Dimethylamino-propyl)-2-methoxy-4-(4-phenoxy-benzoylamino)-benzamide**



N-(*N,N*-dimethylaminopropyl)-4-amino-2-methoxybenzamide was prepared according to the experiment described in **Ex 3**. In a flask were placed PS-DCC (1.2 g, 1.35 mmol/g), dichloromethane (15 µL), 4-phenoxy benzoic acid (0.26 g, 1.2 mmol) and HOBt (0.18 g, 1.35 mmol) and the mixture was gently stirred for 10 minutes before *N*-(*N,N*-dimethylaminopropyl)-4-amino-2-methoxybenzamide (0.20g, 0.80 mmol) was added. The reaction was stirred for three days when PS-trisamine (1.0 g, 3.38 mmol/g) was added. After 2h the resins were filtered off and rinsed with dichloromethane (20 µL). The solvent

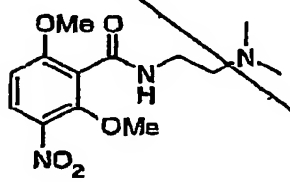
***N*-(2-Diethylamino-ethyl)-2-methoxy-4-[1-methyl-3-(4-phenoxy-phenyl)-ureido]-benzamide**



A solution of compound Ex 32 (0.02 g, 0.051 mmol), EDAC (0.0146 g, 0.076 mmol) and HOBt (0.0089 g, 0.066 mmol) in dichloromethane (3 µL) was stirred at RT for 5 minutes before *N,N*-diethylethylenediamine (0.0086 µL) was added. The resulting reaction mixture was stirred at RT overnight, washed with saturated aq. NaHCO3 solution (3x), brine, dried over MgSO4 and concentrated *in vacuo*. The crude was chromatographed over silica gel (CH_2Cl_2/MeOH/NH_3 ; 90/9/1) to give the title compound as a colourless oil which crystallised upon standing (0.025 g, 0.051 mmol, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (t, 6H), 2.58 (q, 4H), 2.66 (t, 2H), 3.36 (s, 3H), 3.54 (m, 2H), 3.97 (s, 3H), 6.36 (s, 1H), 6.91-7.32 (m, 11H), 8.29 (d, 1H), 8.35 (bs, 1H)

Example 34

***N*-(2-Dimethylamino-ethyl)-2,6-dimethoxy-3-nitro-benzamide**

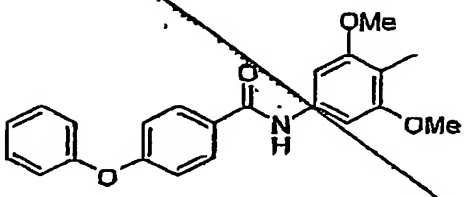


A flask was charged with 2,6-dimethoxy-3-nitrobenzoic acid (1 g, 4.4 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (1.27 g, 6.6 mmol), hydroxybenzotriazole (772 mg, 5.72 mmol) and N,N-dimethylethylene diamine (0.48 µL, 4.4 mmol). Dichloromethane (50 µL) was added and the suspension was stirred under air for 16 h. The now clear reaction mixture was washed consecutively with water (2 x 20 µL) and brine (1 x 20 µL). The organic solution was then briefly dried over sodium sulfate before being filtered and reduced *in vacuo* to give *N*-(*N,N*-dimethylaminoethylamine)-2,6-dimethoxy-3-nitrobenzamide. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04-7.99 (2H, d), 6.77-6.72 (2H, d), 6.50-6.30 (1H, br s, NH), 3.97 (3H, s, MeO), 3.92 (3H, s, MeO), 3.60-3.45 (2H, m), 2.55-2.45 (2H, m), 2.25 (6H, s, Me_2N).

residue was stirred with sodium hydroxide (10 N, 100 µL) for 1 h to form the free aniline, which was collected by filtration. The residues were washed with water (3 x 20 µL) and dried *in vacuo* to give the title compound.

Example 44

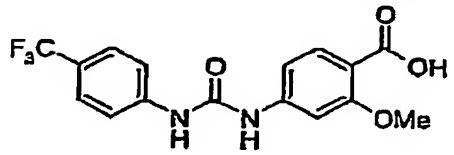
***N*-(3,5-Dimethoxy-4-methyl-phenyl)-4-phenoxy-benzamide**



A flask was charged with Ex 43 (334 mg, 2 mmol), 4-phenoxybenzoic acid (471 mg, 2.2 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (573 m g, 3 mmol) and hydroxybenzotriazole (351 mg, 2.6 mmol). Dichloromethane (20 µL) was added and the suspension was stirred for 100 h. The now clear solution was washed with hydrochloric acid (1 N, 20 µL), sodium bicarbonate (20) and water (20 µL). The organic solution was dried over sodium sulphate, filtered and reduced *in vacuo*. The crude material was chromatographed (Al_2O_3, dichloromethane/methanol/triethylamine, 98:1:1) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88-7.85 (2H, d), 7.75 (1H, s), 7.50-7.40 (2H, m), 7.25-7.15 (1H, m), 7.12-7.05 (4H, m), 6.93 (2H, s), 5.95 (1H, s), 3.85 (6H, s, MeO), 2.09 (3H, s, CH_3).

Example 45

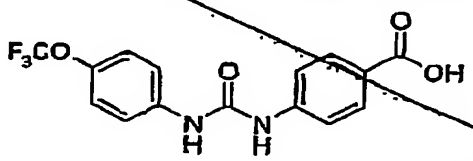
2-Methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzoic acid



To a solution of 4-amino-2-methoxybenzoic acid (3.4 g, 20.3 mmol) in dry dichloromethane (300 mL) under inert atmosphere was 4-trifluoromethylphenyl isocyanate (5.0 g, 26.7 mmol) added drop wise. The reaction was stirred over night at room temperature and a precipitate was formed during the reaction. The precipitate was filtered and washed with dichloromethane and gave 5.7 g (79 %) of the title product. ^{1}H NMR (300 MHz, dmso-d_6): δ 3.8 (s, 3H), 6.9 (dd, 1H), 7.4 (d, 1H), 7.4-7.7 (m, 5H), 9.2 (d, 2H), 12.2 (s, 1H). LCMS(an20n15); RT = 8.306 min, 352.9 m/z

Example 46

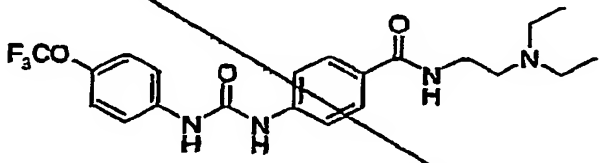
4-[3-(4-Trifluoromethoxy-phenyl)-ureido]-benzoic acid



Using the same procedure as described above was the title product synthesised from 4-amino-benzoic acid (1.2 g, 7.6 mmol) and 4-trifluoromethoxyphenyl isocyanate (2.0 g, 9.8 mmol) giving 2.7 g (quant.) of the product.
LCMS(an20n15); RT = 7.503 min, 338.8 m/z.

Example 47

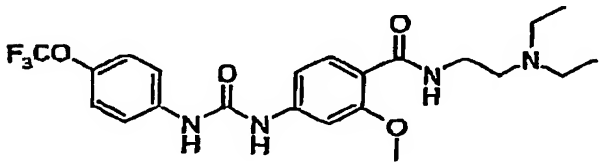
***N*-(2-Diethylamino-ethyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**



To a solution of procainamide (26 mg, 0.112 mmol) in dichloromethane (1.5 mL) under inert atmosphere were triethylamine (31 µL) and 4-trifluoromethoxyphenyl isocyanate (30 µL, 0.145 mmol) added. The reaction was stirred for three days. PS-Trisamine (0.16 g, 3.58 mmol/g, 0.56 mmol) was added and the reaction was stirrede for two more days. The resin was filtered off and the reaction mixture was concentrated *in vacuo*. The crude product was purified by acidic ion exchange chromatography (SCX-colon) giving 29 mg (59%) of the title product. LCMS (an20p10): RT = 5.52 min, (M-1) = 439.0 m/z.

Example 48

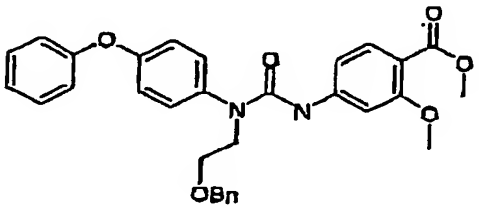
***N*-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**



To a solution of 2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzoic acid (example 153) (50 mg, 0.135 mmol) in dichloromethane (3.5 mL) and dimethylformamide (0.35 mL) was added to polystyrene-DCC (0.5 g, 1.27 mmol/g, 0.64 mmol). Thereafter were HOBT (40 mg, 0.30 mol) and N^1,N^1-diethyl-ethyldiamine (18 µL, 16.5 mg 0.14 mmol) added and

Example 177

4-[3-(2-Benzyloxy-ethyl)-3-(4-phenoxy-phenyl)-ureido]-2-methoxy-benzoic acid methyl ester

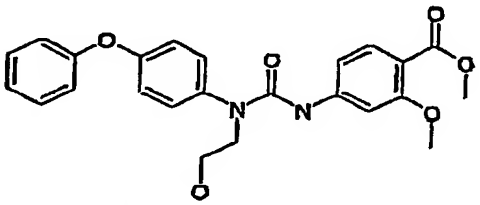


Using the same procedure as described in Ex 169 was the title product synthesised from Ex 176 and methyl 4-amino-2-methoxybenzoate

NMR(CDCl3): δ 3.74 (t, 2H), 4.11 (s, 3H), 4.13 (s, 3H), 3.97 (t, 2H), 4.58 (s, 2H), 6.37 (d, 1H), 7.03 – 7.43 (m, 15H), 7.54 (s, 1H), 7.7 (d, 1H)

Example 178

4-[3-(2-Hydroxy-ethyl)-3-(4-phenoxy-phenyl)-ureido]-2-methoxy-benzoic acid methyl ester

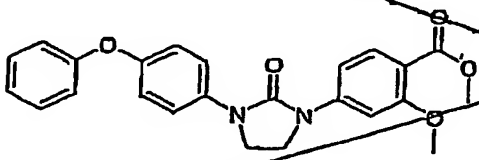


To a solution of Ex 177 (830mg, 1.57 mmol) in methanol (80ml) was added 10% $Pd(OH)_2/C$ (10%w/w, 83mg). The reaction mixture was stirred for 5 hours at 30°C under a hydrogen atmosphere. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give the title compound Ex 178 as a colourless oil (643mg, 1.47 mmol, 93%)

^{1}H-NMR ($CDCl_3$): δ 3.84 (m+s, 5H), 3.9 (m+s, 5H), 6.45 (m, 1H), 7.09 – 7.45 (m, 9H), 7.51 (s, 1H), 7.74 (d, 1H)

Example 179

2-Methoxy-4-[2-oxo-3-(4-phenoxy-phenyl)-imidazolidin-1-yl]-benzoic acid methyl ester

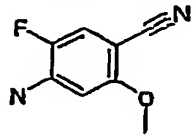


To a cooled (0°C) solution of Ex 178 (640mg, 1.47 mmol) in dry dichloromethane (15ml) were successively added, under an argon atmosphere, methanesulfonyl chloride (0.11ml,

~~LC-MS(an20p10): Rt = 4.75 min. (M+1) = 503 m/z~~

Example 182

4-Amino-5-fluoro-2-methoxy-benzonitrile

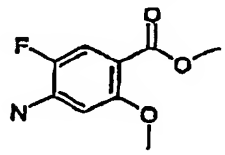


To a cooled (0°C) solution of methanol (5.2ml, 130.0 mmol) in anhydrous THF (30ml) was added, under an argon atmosphere, a 1M solution of *tert* BuOK in THF (25.9ml, 25.9 mmol). After stirring for 5 minutes at room temperature, 4-amino-2,5-difluoro-benzonitrile (2g, 13.0 mmol) was added to the solution in one portion. The reaction mixture was then heated to 70°C and stirred for 2h 30 minutes. After cooling, diethyl ether was added. The organic phase was washed with sat. aq. $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude was chromatographed over silica gel (EtOAc/Heptane: 1/9 to 1/1) to give the title compound **Ex 182** as a pale-yellow solid (1.58g, 9.51 mmol, 73%).

^{1}H-NMR ($CDCl_3$): δ 3.84 (s, 3H), 4.26 (br s, 2H), 6.27 (d, 1H), 7.12 (d, 1H)

Example 183

4-Amino-5-fluoro-2-methoxy-benzoic acid methyl ester

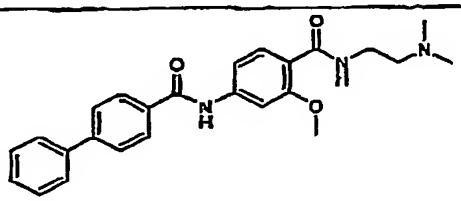
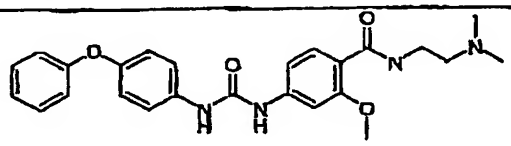
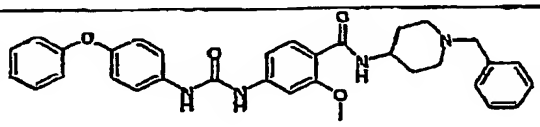
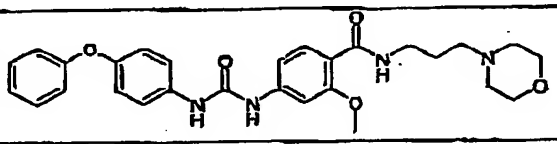
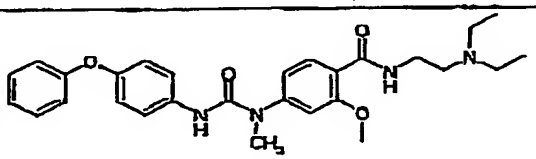
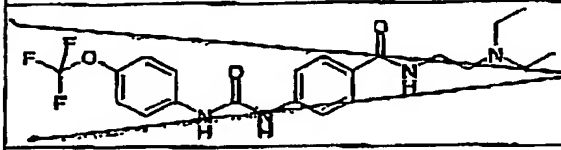
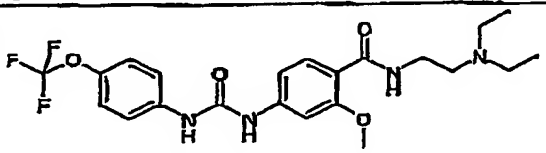
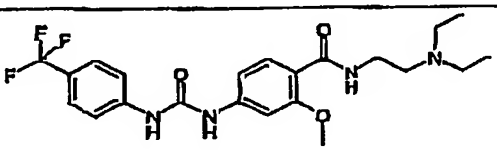
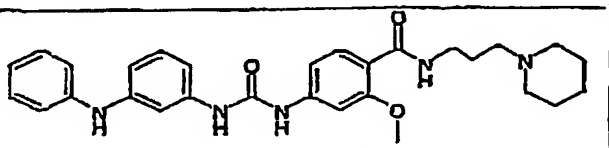
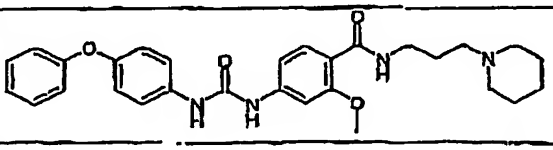


To a saturated solution of gas hydrogen chloride in methanol (20ml) and water (0.04ml) was added **Ex 182** (290mg, 1.74 mmol). The reaction mixture was stirred overnight at 40°C and then at 70°C for 5 hours. Solvent was removed *in vacuo*. The residue was partitioned between sat.aq. $NaHCO_3$ and dichloromethane. The aqueous phase was extracted with dichloromethane (2x). The organic phases were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* .The crude was purified over silica gel chromatography (EtOAc/Heptane: 1/9 to 1/1) to give the title compound **Ex 183** as a white solid (60mg, 0.30 mmol, 17%).

^{1}H-NMR ($CDCl_3$): δ 3.83 (s, 3H), 3.84 (s, 3H), 6.3 (d, 1H), 7.56 (d, 1H)

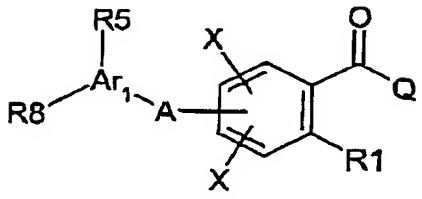
Example 184

5-Fluoro-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzoic acid methyl ester

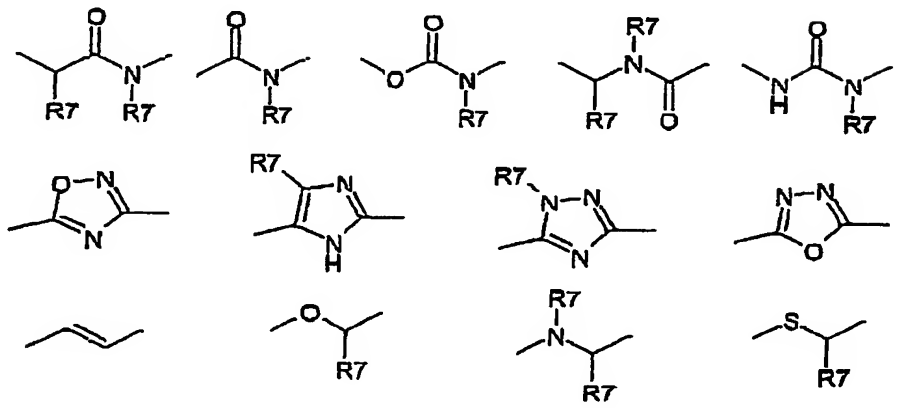
Compound	Example	Receptor binding IC_{50} µM	IP3 IC_{50} µM
	Ex 2	1.48	
	Ex 8	0,38	2.3
	Ex 16	0.22	1.8
	Ex 23	0.21	0.77
	Ex 33	0.048	0.29
	Ex 47	0.07	0.29
	Ex 48	0.096	0.19
	Ex 67	0.027 (SPA)	0.22
	Ex 89	0.012	0.022
	Ex 95	0.044	0.24

CLAIMS

1. A compound with the following structure (Formula I)



wherein -A- is a linker, which is selected from the group consisting of



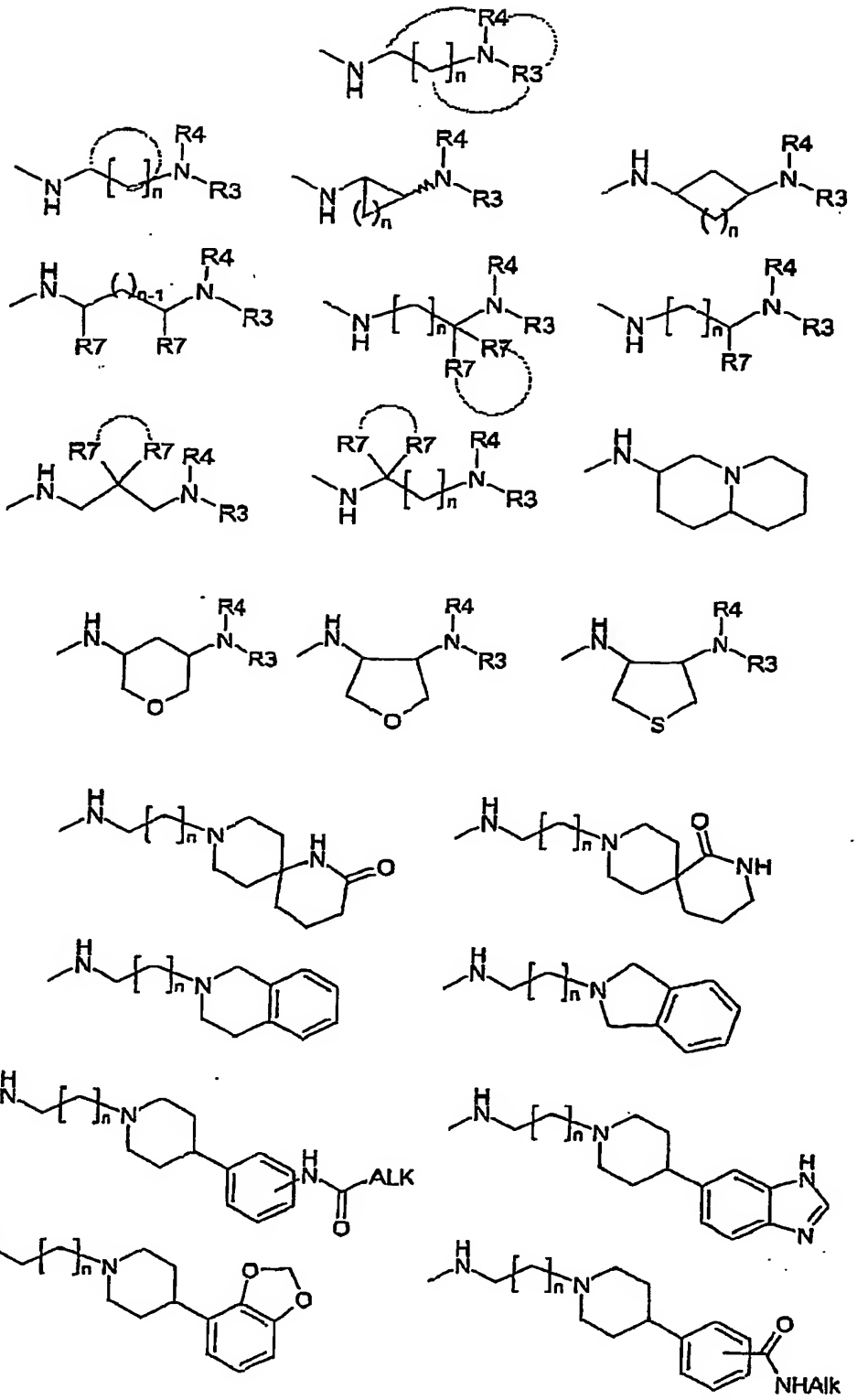
and, wherein the linker -A- may be attached *via* either of the two free bonds to the Ar_1 group;

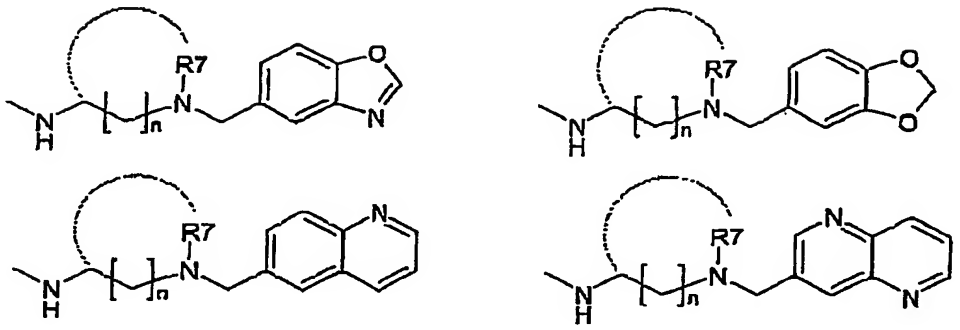
and R7 is the same or different and is hydrogen or a straight or branched C_1-C_4 alkyl or alkenyl group;

Ar_1 is an aryl or heteroaryl group selected from the group consisting of phenyl, pyridine, pyrimidine, pyrazine, thiophene, oxazole, isothiazole, pyrazole, pyrrole, imidazole, indole, benzimidazole, quinoline, isoquinoline, furan, benzofuran, benzothiophene, benzothiazole, indazole, thiazole, isoxazole, oxadiazole and indan;

R1 is a lower alkoxy group alkyl-O- with one to four carbon atoms and preferably one carbon,

Q is selected from the group consisting of





R3 and R4 are the same or different selected from straight or branched alkyl, alkenyl or alkynyl groups with 1-8 carbon atoms; cycloalkyl groups with 3-7 carbon atoms; alkylcycloalkyl with 4-9 carbon atoms; alkylaryl groups selected from the group consisting of benzyl, 2-ethylphenyl, 3-propylphenyl, 4-butylphenyl; alkylheterocyclyl groups selected from the group consisting of 2-ethylpiperazine, 3-propylpiperidine; alkylheteroaryl groups; the aryl, heterocyclyl and heteroaryl groups may be substituted with substituents selected from the group consisting of Alk-CONH-, Alk-O-, HO-, NC-, AlkNH-, Alk_2N-, $-CONH_2$, -CONHAlk, $-CONAlk_2$, aryl, substituted aryl, benzyl, substituted benzyl groups

Alk is the same or a different alkyl, alkenyl or alkynyl group;

R3 and R4 may optionally be linked to each other, when possible, as indicated in Formula I; and oxygen or nitrogen atoms may be inserted in the chain or ring in a chemically stable position;

R5 is selected from the group consisting of hydrogen, halogen atoms, alkoxy groups (AlkO-), hydroxy, alkylamino groups (AlkNH-), dialkylamino groups (Alk_2N-), hydroxylalkyl groups, carboxamido groups ($-CONH_2$, -CONHAlk, $-CONAlk_2$), acylamido groups (-NHCO-Alk), acyl groups (-CO-Alk), -CHO, nitrile, alkyl, alkenyl or alkynyl groups, $-SCH_3$, and partially or fully fluorinated alkyl, alkoxy or thioalkoxy groups including $-CH_2CF_3$, $-CF_2CF_3$, $-CF_3$, $-OCF_3$, $-SCF_3$; $-SO_2NH_2$, $-SO_2NHAlk$, $-SO_2NAlk_2$, $-SO_2Alk$;

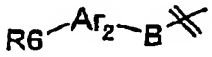
more than one R5 group, same or different, may be present on Ar_1; when more than one R5 or when one R5 and one R8 group are present they could be connected to each other, directly or with a suitable connecting moiety, to form rings;

X being the same or different H or F;

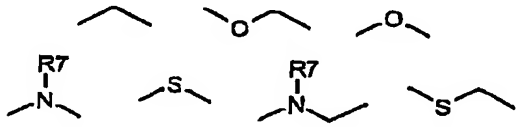
n is 1.2 or 3,

R8 is halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups with 3-7 carbons, aryl groups (Ar), heteroaryl groups, heterocyclyl groups, alkylcycloalkyl groups, alkylaryl groups, alkylheterocyclyl groups, alkylheteroaryl groups, arylalkoxy groups (e.g. $ArCH_2O$-), aryloxy groups (ArO-), alkoxy groups (AlkO-), dialkylamino groups (Alk_2N-), -CONHAlk, -CONHAr -$CONAlk_2$, -NHCO-Alk, -NHCO-Ar, -CO-Alk, -CO-Ar, $-SCH_3$, partially or fully fluorinated alkyl, alkoxy or thioalkoxy groups including $-CH_2CF_3$, $-CF_2CF_3$, $-CF_3$, $-OCF_3$, $-SCF_3$;

or R8 has the structure



in which B is a single bond or a connecting moiety selected from the group consisting of:



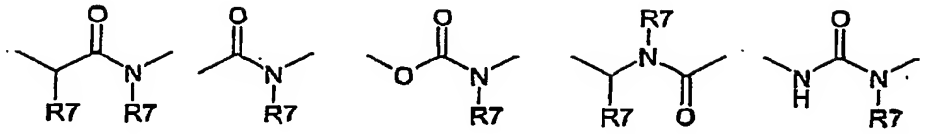
which may be attached *via* either of the two free bonds to the Ar_1 group;

Ar_2 is an aryl or heteroaryl group selected from the group consisting of phenyl, pyridine, pyrimidine, pyrazine, thiophene, oxazole, isothiazole, pyrazole, pyrrole, imidazole, indole, benzimidazole, quinoline, isoquinoline, furan, benzofuran, benzothiophene, benzothiazole, indazole, thiazole, isoxazole, oxadiazole and indan;

R6 is selected from the group consisting of hydrogen, halogen atoms, alkoxy groups (AlkO-), hydroxy, alkylamino groups (AlkNH-), dialkylamino groups (Alk_2N-), hydroxylalkyl groups, carboxamido groups ($-CONH_2$, -CONHAlk, $-CONAlk_2$), acylamido groups (-NHCO-Alk), acyl groups (-CO-Alk), -CHO, nitrile, alkyl, alkenyl or alkynyl groups, $-SCH_3$, and partially or fully fluorinated alkyl, alkoxy or thioalkoxy groups including $-CH_2CF_3$, $-CF_2CF_3$, $-CF_3$, $-OCF_3$, $-SCF_3$, $-SO_2NH_2$, $-SO_2NHAlk$, $-SO_2NAlk_2$, $-SO_2Alk$;

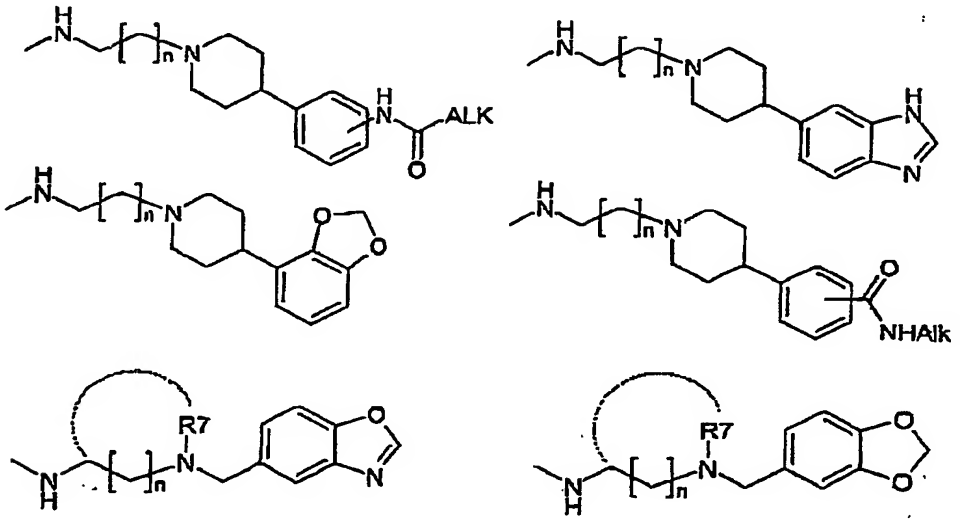
more than one R6 group, same or different, may be present on Ar_2; when more than one R6 group is present they could be connected to each other to form rings.

2. A compound according to claim 1, wherein A is selected from the group consisting of



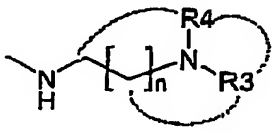
wherein R7 is as defined in claim 1.

3. A compound according to claim 1 or 2, wherein Q is selected from the group consisting of



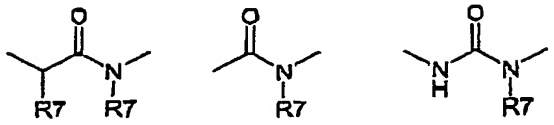
wherein R7 and n is as defined in claim 1.

4. A compound according to claim 1 or 2, wherein Q is



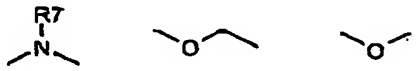
wherein R3, R4 and n are as defined in claim 1.

5. A compound according to any of the preceding claims, wherein A is selected from the group consisting of

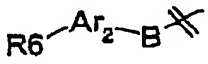


wherein R7 is as defined in claim 1.

6. A compound according to any of the preceding claims, wherein B is a single bond or a connecting moiety selected from the group consisting of



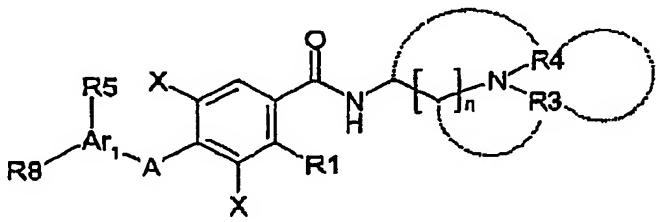
7. A compound according to any of the preceding claims, wherein R8 is



8. A compound according to any of claims 1-6, wherein R8 is selected from the group consisting of halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups with 3-7 carbons, aryl groups (Ar), heteroaryl groups, heterocyclyl groups, alkylcycloalkyl groups, alkylaryl groups, alkylheterocyclyl groups, alkylheteroaryl groups, arylalkoxy groups (e.g. $ArCH_2O$-), aryloxy groups (ArO-), alkoxy groups (AlkO-), dialkylamino groups (Alk_2N-), -CONHAlk, -CONHAr -$CONAlk_2$, -NHCO-Alk, -NHCO-Ar, -CO-Alk, -CO-Ar, -SCH_3, and partially or fully fluorinated alkyl, alkoxy or thioalkoxy groups including -CH_2CF_3, -CF_2CF_3, -CF_3, -OCF_3, -SCF_3.

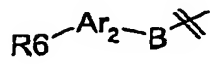
9. A compound according to any of claims 1-6 or 8, wherein R5 is H and R8 is halogen or partially or fully fluorinated alkyl, alkoxy or thioalkoxy groups including -CH_2CF_3, -CF_2CF_3, -CF_3, -OCF_3, -SCF_3;

10. A compound according to any of the claims 1-2, 4-9 with the following structure



wherein Ar_1, Ar_2, A, B, R1, R3, R4, R5, R6, R7, R8, X and n are defined as in claim 1.

11. A compound according to claim 10, wherein R8 is



12. A compound according to any of claims 1-7, 10-11, wherein the -B- moiety is not placed ortho to the -A- linker.

13. A compound according to any of claims 1-7, 10-12, wherein Ar_1 and Ar_2 are the same or different aryl or heteroaryl groups selected from the group consisting of phenyl, pyridine and thiophene.

14. A compound according to any of claims 1-7, 10-13, wherein R5 and R6 may be the same or different selected from hydrogen, halogen atoms, alkoxy groups (AlkO-), alkyamino groups (AlkNH-), dialkylamino groups (Alk_2N-), carboxamido groups (-$CONH_2$, -CONHAlk, $CONAlk_2$), acylamido groups (-NHCO-Alk), nitrile, lower alkyl groups, -CF_3, -OCF_3, -SCF_3, -SCH_3.

15. A compound according to any of the preceding claims in amorphous or crystalline form.

16. A compound according to any of the preceding claims in racemic or enantiomeric form.

17. A compound according to any of the preceding claims in the form of a physiologically acceptable salt, complex, solvate or prodrug thereof.

18. A compound according to any of the preceding claims for use in medicine.

19. A compound according to any of the preceding claims for use in preventing or treating diseases caused by or involving a melanin-concentrating hormone.

20. A compound according to any of the preceding claims for use in modulating the activity of an MCH receptor.

21. A compound according to claim 20, wherein the modulating activity is an antagonistic activity against an MCH receptor.

22. A compound according to claim 20, wherein the modulating activity is an agonistic, inverse agonistic or allosteric activity against an MCH receptor.

23. A compound according to any of the preceding claims, wherein the MCH receptor has at least about 80% such as, e.g. at least about 85% or at least about 90% homology to the amino acid sequence CTLITAMDAN or CTIITSLDTC

24. A compound according to any of the preceding claims, wherein the MCH receptor comprises the amino acid sequence CTLITAMDAN or CTIITSLDTC.

25. A compound according to any of the preceding claims, wherein the MCH receptor is an MCH1 or MCH2 receptor.

26. A compound according to any of the preceding claims, wherein the MCH receptor is an MCH1 receptor.

27. A compound according to any of the preceding claims, wherein the MCH receptor is a mammalian such as human receptor.

28. A compound according to any of the preceding claims for use in preventing or treating feeding disorders.

29. A compound according to any of claims 1-21 or 23-28 for use in reducing body mass.

30. A compound according to any of claims 1-21 or 23-29 for use in preventing or treating Syndrome X (metabolic syndrome), or any combination of obesity, insulin resistance, dyslipidemia, impaired glucose tolerance and hypertension.

31. A compound according to any of claims 1-21 or 23-29 for use in preventing or treating Type II diabetes or Non Insulin Dependent Diabetes Mellitus (NIDDM).

32. A compound according to any of claims 1-21 or 23-31 for use in preventing or treating bulimia, obesity and/or bulimina nervosa.

33. A compound according to any of claims 1-27 for use as an antidepressant and/or anti-anxiety agent.

34. A cosmetic method for reducing overweight and/or for treating of and/or preventing overweight, bulimia, bulimia nervosa, obesity and/or complications thereto, the method comprising administering to an animal such as, e.g. a human in need thereof, an effective amount of a compound as defined in any of claims 1-21 or 23-32.

35. A method for the treatment and/or prophylaxis of diseases caused by a melanin-concentrating hormone, the method comprising administering to a mammal in need thereof an efficient amount of a compound as defined in any of claims 1-33.

36. A method for the treatment and/or prophylaxis of diseases caused by feeding disorders, the method comprising administering to a mammal in need thereof an efficient amount of a compound as defined in any of claims 1-32.

37. A method for modifying the feeding behaviour of a mammal, the method comprising administering to a mammal in need thereof an efficient amount of a compound as defined in any of claims 1-32.

38. A method for the reduction of body mass, the method comprising administering to a mammal in need thereof an efficient amount of a compound as defined in any of claims 1-23 or 23-32.

39. A method for the treatment and/or prophylaxis of Syndrome X (metabolic syndrome) or any combination of obesity, insulin resistance, dyslipidemia, impaired glucose tolerance and hypertension, the method comprising administering to a mammal in need thereof an efficient amount of a compound as defined in any of claims 1-23 or 23-32.

40. A method for the treatment and/or prophylaxis of Type II diabetes or Non Insulin Dependent Diabetes Mellitus (NIDDM), the method comprising administering to a mammal in need thereof an efficient amount of a compound as defined in any of claims 1-23 or 23-32.

41. A method for the treatment and/or prophylaxis of bulimia, bulimia nervosa and/or obesity, the method comprising administering to a mammal in need thereof an efficient amount of a compound as defined in any of claims 1-23 or 23-32.

42. A method for the treatment and/or prophylaxis of depression and/or anxiety, the method comprising administering to a mammal in need thereof an efficient amount of a compound as defined in any of claims 1-22 or 33.

43. A pharmaceutical composition comprising a compound as defined in any of the claims 1-33 or a physiologically acceptable salt thereof together with one or more physiologically acceptable excipients.

44. A pharmaceutical composition according to claim 43, wherein the compound is present in the form of a physiologically acceptable salt such as a salt formed between the compound and an inorganic acid such as e.g., a hydrochloride, a hydrobromide, a hydroiodide, a nitrate, a nitrite, a H_3PO_3 salt, a H_3PO_4 salt, a H_2SO_3 salt, a sulfate, a H_2SO_5 salt, or a salt formed between the compound and an organic acid such as organic acids like e.g. H_2CO_3, acetic acid, C_2H_5COOH, C_3H_7COOH, C_4H_9COOH, $(COOH)_2$, $CH_2(COOH)_2$, $C_2H_5(COOH)_2$, $C_3H_6(COOH)_2$, C4H8(COOH)2, $C_5H_{10}(COOH)_2$, fumaric acid, maleic acid, lactic acid, citric acid, tartaric acid, ascorbic acid, benzoic acid, salicylic acid and phthalic acid.

45. A pharmaceutical composition according to claim 43 or 44 for enteral and/or parenteral use.

46. A pharmaceutical composition according to claim 43 or 44 for oral, buccal, rectal, nasal, topical, vaginal or ocular use.

47. A pharmaceutical composition according to any of claims 42-46 in the form of a solid, semi-solid or fluid composition.

48. A pharmaceutical composition according to claim 47 in solid form, wherein the composition is in the form of tablets such as, e.g. conventional tablets, effervescent tablets, coated tablets, melt tablets or sublingual tablets, pellets, powders, granules, or particulate material.

49. A pharmaceutical composition according to claim 47 in semi-solid form, wherein the composition is in the form of a chewing gum, an ointment, a cream, a liniment, a paste, a gel or a hydrogel.

50. A pharmaceutical composition according to claim 47 in fluid form, wherein the composition is in the form of a solution, an emulsion, a suspension, a dispersion, a liposomal composition, a spray, a mixture, or a syrup.

51. A pharmaceutical composition according to any of claims 44-50 comprising a therapeutically effective amount of a compound according to claims.

52. A pharmaceutical composition according to claim 51, wherein the amount is from about 0.001 mg to about 1 g such as, e.g. from about 0.005 to about 750 mg, from about 0.01 to about 500 mg, from about 0.05 to about 500 mg, from about 0.1 to about 250 mg, from about 0.1 to about 100 mg or from about 0.5 to about 50 mg.

53. Use of a compound according to any of claims 1-21 or 23-32 or a pharmaceutically acceptable salt thereof for the manufacture of a cosmetic composition for reducing overweight and/or for treating of and/or preventing overweight, bulimia, bulimia nervosa, obesity and/or complications thereto.

54. Use of a compound according to any of claims 1-33 or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for i) the treatment and/or prophylaxis of diseases caused by a melanin-concentrating hormone, ii) the treatment and/or prophylaxis of diseases caused by feeding disorders, iii) modifying the feeding behaviour of a mammal, iv) the reduction of body mass, v) the treatment and/or prophylaxis of bulimia, bulimia nervosa and/or obesity, or vi) the treatment and/or prophylaxis of depression and/or anxiety.